40. (New) The method of claim 38, wherein said Annexin-based MDR is Annexin I-based.

In the specification:

Please add the abstract, attached on a separate page.

REMARKS

Claims 15-23, 32-33 and 37-40 are in the case.

Claims pending in the application

In the amendment filed November 5, 2001, Applicants notified the Examiner that she had, in her Official Action dated May 4, 2001, erroneously included claims 32 and 33 in those that "are withdrawn from consideration". The Examiner again included claims 32 and 33 in those that "are withdrawn from consideration" in the current Official Action. The Applicants respectfully submit that claims 32 and 33, filed as new claims on February 21, 2001, when responding to the requirement for restriction, are method claims for decreasing Annexin-based MDR, and are pending in the application. Thus, the Applicants respectfully submit that prior to the present response, claims 15-23 and 32-33 were pending in the application.

Oath

A substitute Oath/Declaration is provided herein clearly setting forth the inventors' names.

Abstract

A substitute abstract is provided herein on a separate sheet apart from any other text.

Amendment to the claims

Reconsideration of this Application and entry of the foregoing amendments are requested. Claims 15, 17, 19, 20, 22 and 23 have been amended and claims 37-40 have been added in view of the Office Action and to better define what the Applicants consider their invention, as fully supported by an enabling disclosure. The amendments to the claims are mostly of editorial nature and are aimed at better defining what the Applicants consider their invention. Additional support for the amendments to claim 15 and for new claim 37 (claim corresponding the subject matter cancelled from claim 15) can be found, throughout the specification which indicates that the demonstration of the direct role of P-40 in MDR is at the gist of the invention. Support may be found for instance, at page 4, lines 1-2; on figure 6 and the legend of this figure at page 18, lines 19-24, on

figure 9 and legend to this figure at page 19, lines 23-29; at page 25, lines 9-23; at page 29, line 23 to page 30, line 2; and at page 35, line 25 to page 36, line 5.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 15-23 and 34-36 under 35 U.S.C. § 112, second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

She rejected claim 15 alleging that it "is indefinite because the claim recites 'modulates/modulator' and it is unclear if 'modulates' means increase or decrease as only one term should be recited in the claim". She similarly rejects claim 20 which recites a "method of modulating Annexin-based MDR" in a cell without specifying whether the modulation is up or down. The Applicants respectfully disagree with the Examiner's contention that method claims should only be unidirectional (i.e. an increase or a decrease of activity). Nevertheless, to accelerate the prosecution of the present application, claims 15 and 20 now relate to methods of decreasing MDR in a cell, while new claims 37 and 39 relate to methods of increasing MDR in a cell.

The Examiner further alleges that claim 15 is indefinite because it is difficult to determine what "drug" the affecting compound will be incubated with or

not according to item (a) of the claim. Claim 15 was amended to better convey that the drug with which the MDR cell is incubated is a drug to which the MDR cell is resistant.

She further alleges that claim 15 is indefinite because it fails to clearly delineate an assay which appears required to identify the Annexin-based MDR-affecting compound and that it does not set forth a method step to demonstrate how to assess the effect of the compound or to demonstrate the end point of the method. Applicants believe that these objections have been overcome by the amendments to Claim 15 which clearly defines that the assessment of the effect of a candidate compound on the resistance of an MDR cell to a particular drug is achieved by comparing the resistance of the cell to that drug after it has been exposed to the candidate compound, with that of a control cell which has not bee so exposed to that candidate compound (i.e. in the presence or absence of the candidate compound).

The Examiner rejects claims 17 and 20 as indefinite because they recite "small molecule", a terminology that she finds not specific as to the identity of the material proposed. Applicants submit that this rejection is overcome by the references provided herewith and included in the Information Disclosure Statement. These

references generally show that this terminology is well known in the art and is used to refer to non-peptides drug candidates. See for instance Garrett, 1999 "Discovering Novel Chemotherapeutic Drugs for the Third Millenium" which refers to two earlier articles 1) "Is there a future for the small molecule in developmental cancer therapy", 1992; and 2) "Emerging molecular therapies: small molecule drugs", 1999. See also Jang, 2001 "Pharmacokinetics and Its role in Small Molecule Drug Discovery Research"; Ecker, 1999 "RNA as a small-molecule drug target: doubling the value of genomics"; Nauman, 2001 "Kinetic parameters for small-molecule drug delivery by covalent cell surface targeting"; Strege, 2000 "Mixed Mode Anion-Cation Exchange/Hydrophilic Interaction Liquid Chromatography-Electrospray Mass Spectrometry as an Alternative to Reversed Phase for Small Molecule Drug Discovery". The Applicants also submit that EGTA and Verapamil have formula weights of 380 FW and 491 FW, respectively. They are examples of "small molecules" as this terminology is understood by people of ordinary skill in the art and as specified in the disclosure at page 30, lines 4-7.

The Examiner noted that claim 34 depended on cancelled claim 1. Applicants submit that this rejection is rendered moot by the cancellation of claim 34.

In view of the above and foregoing, it is respectfully requested that the Examiner withdraw her rejection of claims 15-23 and 34-36 under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 102

The Examiner maintains her rejection of claims 15, 19 and 20 under 35 U.S.C. § 102(b). She remains of the opinion that claims 15, 19 and 20 are anticipated by Wang, et al. because "Wang anticipates the claimed invention as Wang identifies a compound (P-40) that affects Annexin-based MDR in a cell in the presence of a drug (Adriamycin and Taxol) and assessed the effect of said compound as claimed in the present application".

The Examiner pointed out twice that she found our arguments unconvincing because claim 15 does not recite P-40 or Annexin: "claim 15 does not recite P-40 [but rather] a method of identifying a compound that modulates Annexin-based multidrug resistance (MDR) in a cell . . ." and "Applicant's contention that Wang neither teaches nor suggests the direct role of Annexin in multidrug resistance is not persuasive as the claims do not recite that".

The Examiner further notes that the references cited in support of the argument that over-expression of a gene in a cell displaying a specific phenotype are not a

reliable proof that the gene causes this phenotype because they were not provided in an Information Disclosure Statement. Please therefore find enclosed an Information Disclosure Statement listing all the references cited in support of our earlier argument.

Claims 15 and 20 have been amended to recite in the preamble that the cell has "been rendered MDR by an expression of an Annexin" and that the decrease is "direct". Similarly, new claims 37 and 39 directed to methods of increasing MDR recite this wording. In view of the above and foregoing, it is respectfully requested that the Examiner withdraw her rejection of claims 15 and 19-20 under 35 U.S.C. § 102(b), first paragraph.

Please find attached Annex A comprising *in vivo* results further confirming results included in the application and generally further confirming that cells transfected with Annexin cDNA demonstrate resistance to anticancer drugs as shown by increased viability of the cells (Figure 1), that antagonists such as antisense Annexin I confers sensitivity to anticancer drugs (Figure 2A); and that the tumors of patients that are responsive to anticancer drugs (adriamycin or taxol) show a low level of expression of Annexin I as compared to those that are non-responsive (Figure 3A).

CONCLUSIONS

The rejections of claims 15-23 and 32-36 are believed to have been overcome by the present remarks, and by the amendments to the claims. From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such an action is earnestly solicited.

In the event that there are any questions concerning the Amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of the application be expedited.

Authorization is hereby given to charge Deposit Account no. 17-0055 for any deficiencies or overages in connection with this Response.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached pages are captioned "**Version with markings to show changes made**".

Respectfully submitted,

Elias Georges, et al.

October 17, 2002

By: _____

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Elias Georges, et al.
Serial No.:	09/529,925
Filed:	07/30/00
For:	P40/ANNEXIN 1 AND RELATED PROTEINS AND THEIR ROLE IN MULTIDRUG RESISTANCE
Group Art Unit	1653
Examiner:	H. Robinson

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 15, 19, 20, 22 and 23, have been amended as follows: Underlines indicate insertions and ~~strikeouts~~ indicate deletions.

15. (Twice amended) A method of identifying a compound that directly decreases Annexin-based multidrug resistance (MDR) in a cell having been rendered MDR by [an] expression of an Annexin, comprising:

a) incubating said cell with a drug to which said cell is resistant in the presence or absence of a candidate compound ~~in the presence or absence of a cytotoxic drug~~; and

b) assessing the effect of said candidate compound on the resistance of said cell to said ~~cytotoxic~~ drug;

wherein a candidate compound is selected ~~as a modulator of Annexin-based MDR~~, when the resistance of said cell to said ~~cytotoxic~~ drug is measurably ~~different~~ lower in the presence of said compound as compared to in the absence thereof.

19. (Twice amended) The method of claim 15, wherein said ~~cytotoxic~~ drug is an anticancer drug.

20. (Amended) A method of ~~modulating~~ directly decreasing Annexin-based MDR in a cell having been rendered MDR by an expression of an Annexin comprising: administering thereto an effective amount of a compound selected from the group consisting of a nucleic acid molecule, a dominant negative mutant of an Annexin, a mutant Annexin protein, an antibody to Annexin, a peptide, and a small molecule, whereby said effective amount of said compound ~~modulates~~ decreases Annexin-based MDR in said cell.

22. (Twice amended) The method of claim ~~35~~ 21, wherein said compound is an Annexin I antisense nucleic acid.

23. (Twice amended) The method of claim ~~35~~ 21, wherein said compound is a calcium chelator or a calcium channel blocker.

Please cancel claims 34 to 36 and add new claims 37 to 40.

37. (New) A method of identifying a compound that directly increases Annexin-based multidrug resistance (MDR) in a cell having been rendered MDR by an expression of an Annexin, comprising:

a) incubating said cell with a drug to which said cell is resistant in the presence or absence of a candidate compound; and

b) assessing the effect of said candidate compound on the resistance of said cell to said drug;

wherein a candidate compound is selected, when the resistance of said cell to said drug is measurably higher in the presence of said compound as compared to in the absence thereof.

38. (New) The method of claim 37, wherein said cell is a cell having been rendered multidrug resistant (MDR) by an expression of an Annexin nucleic acid molecule.

39. (New) A method of directly increasing Annexin-based MDR in a cell having been rendered MDR by an expression of an Annexin comprising: administering thereto an effective amount of a compound selected from the group consisting of a nucleic acid molecule, a dominant positive mutant of an Annexin, a mutant Annexin protein and a peptide, and a small molecule whereby said effective amount of said compound increases Annexin-based MDR in said cell.

40. (New) The method of claim 38, wherein said Annexin-based MDR is Annexin I-based.

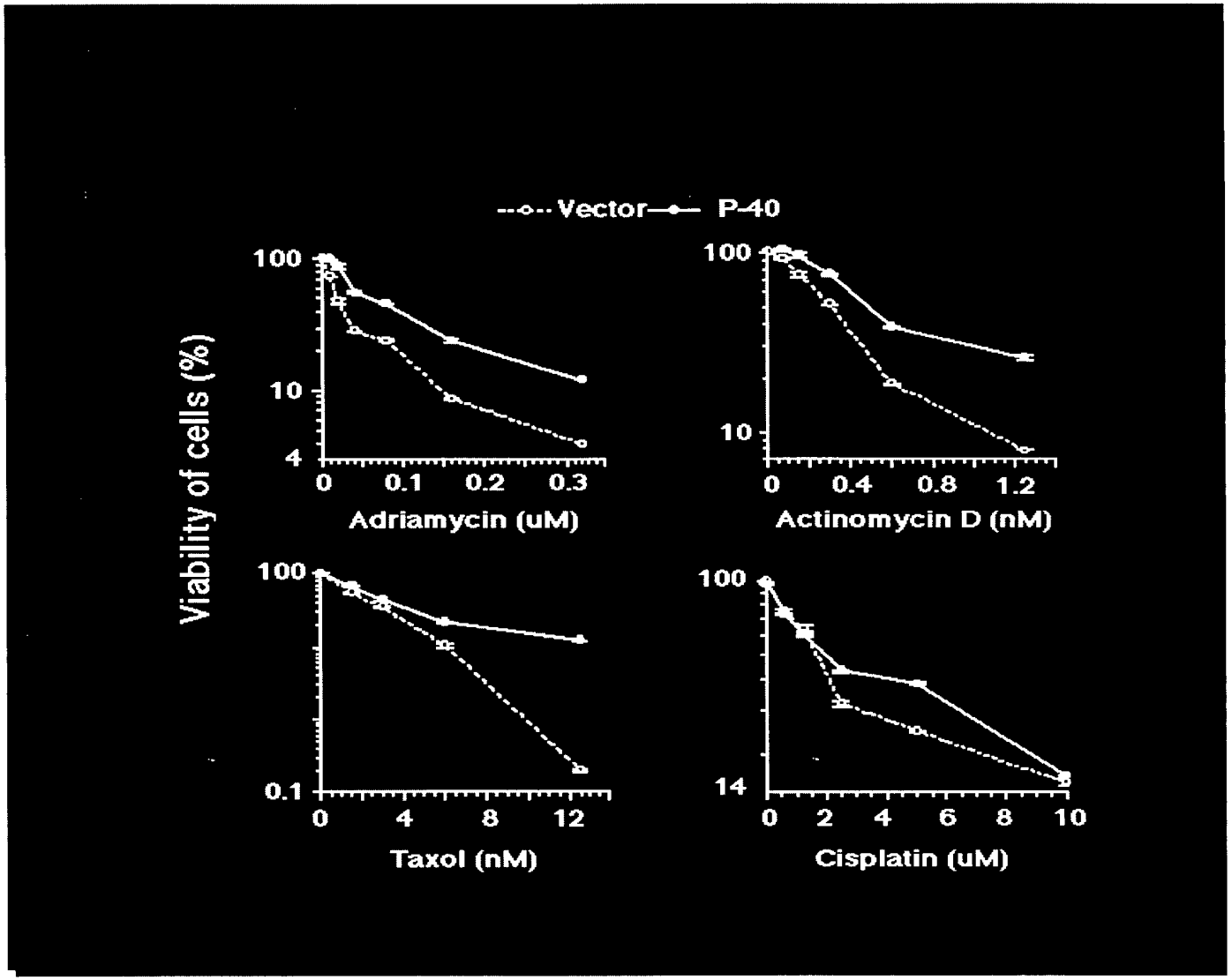
In the Specification:

The abstract on the following page has been added.

Annex A

Transfection of SENSE ANX1 cDNA confers resistance to anticancer drugs

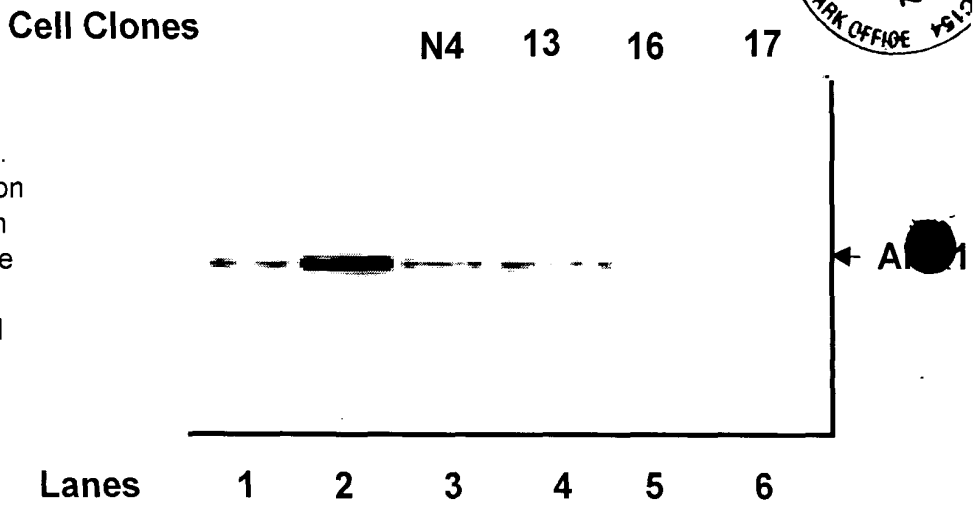
Figure 1



The results in Figure 1 show a cell viability assay of MCF7 breast cancer cells that are transfected with an empty eukaryotic expression Vector therefore do NOT express P40 or Annexin I or are transfected with the same vector containing P-40 or Annexin I full length cDNA. The graphs in the above figure show the viability of cells WITHOUT P40 or Annexin I expression (vector) and WITH P-40 or Annexin I Expression (P-40) in the presence of increasing concentrations of anti-cancer drugs (Adriamycin, Actinomycin D, Taxol, and Cisplatin). Cells expressing P-40 show resistance to anticancer drugs as indicated by enhanced or increased viability.

Transfection of ANTISENSE ANX1 cDNA confers SENSITIVITY to anticancer drugs

Figure 2A

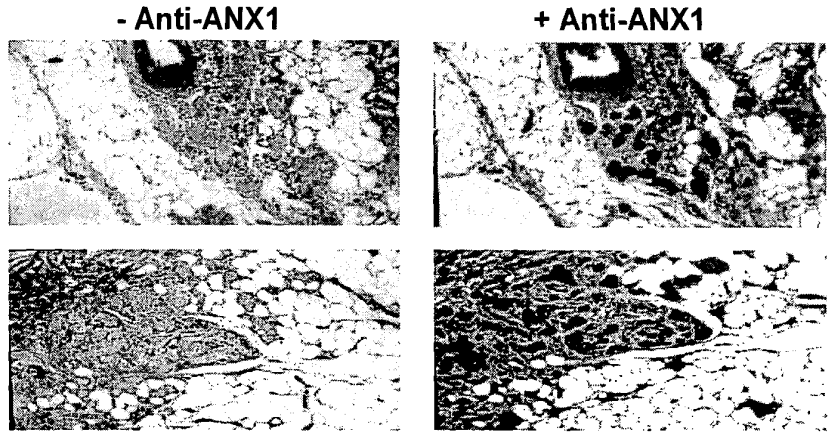


The results in figure 2A show two tumor model cell lines expressing Increasing levels of Annexin I (SKOV3 and SKOV3/VLB or Lanes 1 and 2). Lane 3 shows SKOV3 cells transfected with an empty eukaryotic expression vector alone. Lanes 4-6 show three clones of SKOV3 cells transfected with antisense cDNA encoding Annexin I. Note that the expression of antisense Annexin I decrease expression levels of Annexin I (ANX1) protein in each of the three clones, with clone 17 expression the least amount of Annexin I Protein relative to N4 control.

Table II. *The IC_{50} values derived from growth curves of cytotoxicity experiments comparing the effects of reduced ANX1on the sensitivity of various clones (13, 16 and 17) to anticancer drug (Etoposide, Doxorubcin, and Melphalan). Clone 17 with the lowest ANX1 levels shows 4 - 13 fold increase in sensitivity to anti-cancer drugs.*

	IC_{50} [Fold decrease in IC50 relative to PCIN4]					
Tumor cell clones	**Etoposide**		**Doxorubicin**		**Melphalan**	
PCIN4	2.00 uM	[--]	125.0 nM	[--]	3.0 uM	[--]
Clone 13	0.80 uM	**[2.5]**	50.0 nM	**[2.5]**	1.0 uM	**[3.0]**
Clone 16	0.80 uM	**[2.5]**	40.0 nM	**[3.1]**	1.5 uM	**[2.0]**
Clone 17	0.15 uM	**[13]**	15.0 nM	**[8.0]**	0.7 uM	[4.0]

Figure 3A



The results in figure 3A show immunohistochemical staining of Breast tumor samples from two patients following chemotherapeutic Treatment with adriamycin and taxol. Tissue sections from patients 1 and 2 are either stained with IgG2a and a second antibody (- Anti-ANX1) or anti-Annexin monoclonal antibody (IPM96) and a second antibody (+ Anti-ANX1). The dark brown staining seen With patients 1 and 2 show positive expression or high expression of Annexin 1 (ANX1) in these two tumors.
The study described below is a double blind study that was done on 28 patients with advanced metastatic breast cancer. The results Of this study was described in an abstract at the ASCO meeting in Orlando in 2002.

Summary of Clinical Assessment of ANX1Expression in Responsive and Non-responsive Breast Tumors

Intensity	Non-responders	Responders	Total
-	1	10	11
1 (+)	3	6	9
2 (++)	1	3	4
3 (+++)	3	1	4
Total	8	20	28

Table I. *The results of immunohistochemical staining (IHC) intensity versus response status of the 28 patients. [table] Chi - square test of (0,1) versus (2,3) Numerical value = 5.18 P < 0.025 Higher IHC intensity of P-40 or Annexin I is associated with drug resistance in first-line adriamyci n / taxol treatment of metastatic breast cancer.*